REMARKS

Upon entry of this amendment, Claims 1-12, 15-34, 37, 43-47, 50-54, 56-58, 60, 61, 63-77, and 97-102 are pending. Among them, Claims 7 and 75-77 are withdrawn for being directed to non-elected inventions.

Applicants note that the IDS filed on 8/6/04 and 9/30/05 have been considered by the Examiner.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Restriction

The Examiner has made the restriction requirement Final. But the Examiner also indicates that if a product claim is found allowable, withdrawn process claims (such as Claims 75-77) that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04.

Drawings

The Office Action indicates that no color drawings will be accepted unless a petition under 37 C.F.R. § 1.84(a)(2) is granted.

Applicants' attorney Yu Lu interviewed the Examiner on October 31, 2007, and indicated that Applicants will submit a set of black and white drawings to obviate the need to submit formal color drawings. The Examiner agreed to this suggested approach. This response also constitutes the substantive statement required under 37 C.F.R. § 1.133(b).

Applicants submit herewith a set of black and white drawings to replace the originally submitted drawings.

Claim Objections

Claims 1, 31, 43, 44, 47, 60, 67, and 102 are objected to because of alleged informalities.

Regarding the objections to Claims 1, 43, and 44, while not necessarily agree with the Examiner's objections, Applicants have amended these claims to improve form. No new matter is introduced and these amendments do not narrow the scope of the claims. Reconsideration and withdrawal of the objections are respectfully requested.

Claim 31 is objected to for reciting "by," which the Examiner argues that it is "inadvertently inserted." Applicants submit, however, "by" is intended to be in the claims, since the transcription factor can bind to the promoter either by the binding site or to the binding site. Thus reconsideration and withdrawal of the objections are respectfully requested.

Claims 47 is objected to for improperly depending on Claim 46. Applicants have amended Claim 47 to depend on Claim 44 in order to obviate this objection.

Claim 60 is objected to for reciting "a nucleic acid segment encoding a regulatory protein," which allegedly may be confused with the first and second nucleic acid segments. While not acquiescing in the Examiner's objection, Applicants have amended Claim 60 to advance prosecution. As a result, Claim 61 is also amended. These amendments do not narrow claim scope.

Claim 67 is objected to for reciting "a response element." Applicants have adopted the Examiner's suggestion to amend Claim 67 to recite "the response element."

Claim 102 is objected to for reciting "at least two nucleic acid segments." Applicants have adopted the Examiner's suggestion to amend Claim 102 to recite "at least two additional nucleic acid segments."

In view of the foregoing, all claim objections are overcome. Reconsideration and withdrawal of the objections are respectfully requested.

Claim rejection under 35 U.S.C. § 101

Claim 8 is rejected for allegedly claiming non-statutory subject matter, because the claim allegedly read on a human being.

Applicants have amended Claim 8 to recite "isolated (cell)" to overcome this rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejection under 35 U.S.C. § 112, second paragraph

Claims 2, 25, and 30 are rejected for allegedly being indefinite, because "Claims 1 and 20 do not actually include a binding site operably linked to the recombinant pol III promoter."

While not acquiescing in the reasoning of the Office Action, Applicants have amended Claims 2, 25, and 30 to obviate this rejection.

Claim 5 is rejected for allegedly being vague, because "the metes and bounds of 'comprising the nucleic acid sequence as set forth in SEQ ID NO: 1' are unclear."

Applicants submit that Claim 5 is directed to a nucleic acid within the scope of Claim 4, which comprises the first and second nucleic acid segments of claim 1. Claim 5 further requires the nucleic acid to comprise SEQ ID NO: 1. Thus in the broadest sense, the claimed nucleic acid can comprise SEQ ID NO: 1 in addition to the first and second nucleic acid segments of claim 1, although SEQ ID NO: 1 itself also comprises the first and second nucleic acid segments of claim 1. Applicants submit that there is nothing ambiguous about this claim. Reconsideration and withdrawal of the indefiniteness rejection are respectfully requested.

Claim 22 is rejected for allegedly having no antecedent basis for "the DNA binding domain."

Applicants have amended Claim 22 to depend on Claim 20, which provides proper antecedent basis for "the DNA binding domain."

Claim 34 is rejected for allegedly having no antecedent basis for "the polymerase III promoter element."

Applicants have amended Claim 34 to recite "polymerase III promoter," thereby providing proper antecedent basis for amended Claim 34.

Claims 53 and 54 are allegedly vague because "the metes and bounds of 'transgene comprises a hairpin RNA (ribozyme)' are unclear."

While not acquiescing in the reasoning of the Office Action, Applicants have amended Claims 53 and 54 to obviate this rejection.

Claim 61 is allegedly vague because "the metes and bounds of 'a regulatory protein

which promoters [sic] transcription from the regulated promoter' are unclear." The Examiner argues that it is unclear what the relationship of the regulatory protein to the transcription factor is (*i.e.*, whether the regulatory protein is in addition to the transcription factor or if they are the same."

Applicants submit that there is nothing vague in Claim 61, since the regulatory proteins (such as the RXR and VgEcR proteins used to promote the transcription from the regulated promoter E/GRE HSmin) are clearly distinct from the transcription factor (such as the GAL-Oct transcription factor used to regulate the recombinant polymerase III promoter). Reconsideration and withdrawal of the rejections are respectfully requested.

Claim 66 is rejected as allegedly lacking antecedent basis for "a response element." While not acquiescing in the reasoning of the Office Action, Applicants have amended Claim 66 to obviate this rejection.

In view of the foregoing, all claim rejections under 35 U.S.C. § 112, second paragraph are overcome. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim rejection under 35 U.S.C. § 102

Claims 1, 2, 4, 8-12, 15-22, 25-33, 37, 43-45, 47, 50, 57, 58, 60, 61, 63-74, 97, and 99 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Evans *et al.* (US 2002/0177564, or "Evans").

The Examiner broadly interprets "polymerase III promoter" as including "an interpretation that the recombinant pol III promoter is any portion of the promoter in combination with any other promoter for example a TATA element as demonstrated in Figure 2 (of Evans)." Thus interpreted, the Examiner argues that Evans teaches an RNA polymerase III promoter operably linked to at least 4 ecdysone response elements, which are responsive to transcription factors such as RXR and VgEcR. Applicants respectfully disagree.

Pursuant to MPEP 2111: "[d]uring patent examination, the pending claims must be 'given their broadest reasonable interpretation consistent with the specification.' The Federal Circuit's *en banc* decision in *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir.

2005) expressly recognized that the USPTO employs the 'broadest reasonable interpretation' standard" (emphasis added).

Therefore, the "broadest reasonable interpretation" standard not only requires the Examiner to give the claims their "broadest" interpretation, but also requires the Examiner's interpretation to be both "reasonable" and "consistent with the specification."

Applicants submit that the Examiner's interpretation of the term "polymerase III promoter" is neither reasonable nor consistent with the specification. According to the Examiner's interpretation, "polymerase III promoter" means "any portion of the promoter in combination with any other promoter, for example, a TATA element."

This interpretation is not reasonable, because it completely does away with the explicit reference to "pol III" in the term. The Examiner argues that "polymerase III promoter encompasses a variety of promoters whose relationship to pol III is not stated," and there is allegedly a "lack of structural requirements of the recombinant pol III." However, even if this is true (which Applicants disagree), the Examiner still has not provided a reasonable interpretation that includes "Pol III." The Examiner's interpretation above renders "Pol III" completely superfluous.

Applicants submit that one of skill in the art would understand that, when *reasonably* interpreted, the term "pol III promoter" means a promoter that can be used by an RNA polymerase III to initiate transcription. This interpretation is also consistent with the claim interpretation canon of giving claims their "plain meaning (unless inconsistent with the specification)" *See* MPEP 2111.01:

> "During examination, the claims must be interpreted as broadly as their terms reasonably allow. *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1369, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004). ... This means that the words of the claim must be given their plain meaning unless the plain meaning is inconsistent with the specification. *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989); *Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1372, 69 USPQ2d 1857 (Fed. Cir. 2004) (Ordinary, simple English words whose meaning is clear and unquestionable, absent any indication that their use in a particular context changes their meaning, are construed to mean exactly what they say." (emphasis added)

Applicants submit that the plain meaning of "pol III promoter" means that the promoter is one that can be used by "(RNA) polymerase III," and there is nothing in the specification which indicates that it should have a different meaning.

Applicants further submit that the Examiner's interpretation is also inconsistent with the specification. The instant specification explicitly and repeatedly teaches that RNA polymerase III promoters (as opposed to any other promoters, such as Pol I or Pol II promoters) are to be used in the claimed invention. The Examiner's interpretation expansively reads the term to mean any kind of promoters, which directly contradicts the teachings of the instant specification.

Therefore, Applicants submit that, under the "broadest reasonable interpretation," the claimed invention recites a "recombinant polymerase III promoter," which is a promoter that can be used by RNA polymerase III to initiate transcription.

Applicants further submit that, under this interpretation, Evans fails to disclose a recombinant polymerase III promoter, and thus cannot anticipate the claimed invention.

Specifically, Evans describes the use of a recombinant Pol II promoter for expressing exogenous gene or cDNA in a mammalian host. The recombinant Pol II promoter "comprise at least a minimal promoter in combination with an ecdysone response element. A minimal promoter, when combined with an enhancer region (e.g., a hormone response element), functions to initiate mRNA transcription in response to a ligand/receptor complex." See paragraph **[0165]** of Evans, and also Figure 2 of Evans.

As a skilled artisan will appreciate, Pol II (rather than Pol I or Pol III) promoters are used by mammalian cells to synthesize most (if not all) mRNA, such as the exogenous genes intended to be transcribed into mRNA in Evans.

In contrast, RNA Polymerase I is used to transcribe rRNA (Ribosomal RNA, such as the 18S, the 5.8S, and the 28S rRNA molecules of the eukaryotic ribosome) in large quantity (Pol I conducts 80% of all transcription in the cell). The process of transcription by Pol I is relatively unregulated, because rRNA for ribosomes is almost always needed in large quantities for protein synthesis.

On the other hand, RNA Polymerase III transcribes a limited number of genes to

synthesize ribosomal 5S rRNA, tRNA and other small RNAs (but not mRNA for proteins). In general, the genes transcribed by RNA Pol III fall in the category of "housekeeping" genes whose expression is required in all cell types and most environmental conditions, and the regulation of Pol III transcription is primarily tied to the regulation cell growth and the cell cycle, thus requiring fewer regulatory proteins than RNA polymerase II.

Therefore, these three types of RNA polymerases perform distinct cellular functions, and the corresponding *promoters* used by these distinct RNA polymerases (to initiate transcription from the respective genes) have also evolved to comprise distinct structural features not shared among one another.

For example, the U6 snRNA promoter (a Pol III promoter) may comprise: (1) a TATA box centered about 26 base pairs upstream of the transcription start site, (2) a PSE (**P**roximal **S**equence **E**lement) centered approximately 55 base pairs upstream of the transcription start site, and (3) an enhancer-like DSE (**D**istal **S**equence **E**lement) at least 200 base pairs upstream of the transcription start site. In operation, **SNAPc** (**SN**RNA **A**ctivating **P**rotein **c**omplex, also termed PBP and PTF) first binds to the PSE, and then acts to assemble the transcription factor **TFIIIB** at the TATA box. Once assembled at the TATA box, TFIIIB recruits Pol III at the transcription start site, which proceed to transcribe the operably linked gene (such as the U6 snRNA).

During this sequence of events, the assembly of **SNAPc** at the PSE is greatly stimulated by the Pol II transcription factors Oct1 and STAF that bind to DSE. There is no evidence, however, that other transcription factors (such as RXR:VgEcR used in Evans) can function like Oct1 to stimulate SNAPc assembly at PSE.

Therefore, in the Evans construct, such as the one described in Figure 2, there is no "recombinant polymerase III promoter" as recited in the claimed invention. There is no evidence that the Evans promoter can be used by any RNA Pol III. Even if the minimal promoter in Evans may contain a TATA box, as the Examiner suggests, there is no evidence that there is any PSE that can assemble SNAPc, which is a pre-requisite for TFIIIB binding to the TATA box in the U6 Pol III promoter. There is also no evidence that RXR:VgEcR, when bound to the EcRE repeats in Figure 2 of Evans, can stimulate SNAPc binding to PSE (if present at all).

In contrast, Evans itself lists many Pol II promoters suitable for its constructs in paragraph **[0170]**, including an explicit recitation of "RNA Pol II promoter." Conspicuously missing is any reference to "RNA Pol III promoter."

Therefore, the weight of the evidence favors Applicants' assertion that Evan fails to teach or suggest any "recombinant polymerase III promoter," and thus Evans cannot anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-4, 11, 25, 28-31, 33, 34, 37, 43, 50-52, 56, 58, 60, 63-73, 98, and 99 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Li *et al.* (US 2004/0146858, or "Li").

The Office Action argues that Li teaches an RNA Pol III promoter (a mammalian U6 promoter) operably connected to a tetO site, and that "a tet repressor is under expression of an inducible promoter."

Applicants submit that Li cannot anticipate the claimed invention, because the tet repressor is not a "transcription factor (that) increases transcription from the recombinant polymerase III promoter."

As the Examiner points out, the disclosed tet repressor is a transcription repressor. Thus, even assuming for the sake of argument that the tet repressor is a "transcription factor," it decreases, rather than increases transcription from the recombinant polymerase III promoter (i this case, U6 promoter). See paragraph **[0112]** of Li:

> When tet O is bound by a tetracycline-sensitive trans-acting protein (tetracycline repressor, Tet R), transcriptional initiation at the promoter is prevented. When tet O is not bound by Tet R, transcription from the promoter can proceed, allowing expression of the coding sequence operably linked to it (see: Ohkawa and Taira, Human Gene therapy, 11:577-585 (2000); van de Wetering, EMBO Reports, 4:609-615 (2003). (emphasis added)

Thus, Li cannot anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejection under 35 U.S.C. § 103(a)

Claim 46 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Evans (of record) as applied to Claims 1, 2, 4, 8-12, 15-22, 25-33, 37, 43-45, 47, 50, 57, 58, 60, 61, 63-74, 97, and 99 above, and further in view of Cheng *et al.* (*Gene Therapy* 4: 1013-1022, 1997).

The Office Action argues that Evens fails to teach the use of GFP as a reporter, while Cheng allegedly makes up this deficiency.

As argued above, Applicants submit that Evan fails to teach any recombinant Pol III promoter recited in the claims, and Cheng does not make up this deficiency. Thus even assuming for the sake of argument that Evans can be combined with Cheng, the combined teaching still fails to teach or suggest all the elements of the claimed invention.

Since a dependent claim cannot be obvious if the independent claim from which it depends is not anticipated and not obvious, Applicants submit that all pending claims, including Claim 46, are not obvious in view of Evan and Cheng.

Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSIONS

Applicants believe this application is in condition for allowance in view of the foregoing.

Applicants believe no fee in addition to those listed in the accompanying amendment transmittal (filed concurrently herewith) is due with this response. However, if any other fee is due, please charge our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw under Order No. **CSHL-P01-012**.

Dated: November 5, 2007

Respectfully submitted,

By_____

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